

## REMARKS

### Introduction

Claims 32, 34, 37-44, 46, 49-56, 58, 60-69, 73, 74, 78, 79, and 83 are pending in the above-referenced application. In an Advisory Action mailed on June 6, 2006, Claims 40-43, 52-55, 64, 65, 67, 68, 73, 78, and 83 were objected to. Claims 32, 34, 37-39, 44, 46, 49-51, 56, 58, 60-63, 66, 69, 74, and 79 were rejected under 35 U.S.C. § 103.

As a preliminary matter, Applicant notes that the Advisory Action indicated that a reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal (Advisory Action, Box 1). Although Applicant filed an Amendment After Final on May 19, 2006, Applicant did not file a Notice of Appeal, and believes that this notation may be in error.

Claims 32, 44, and 56 have been amended. In view of the foregoing amendment of claims, Applicant respectfully requests reconsideration and allowance of all claims pending in the application.

### Claim Rejection Under 35 U.S.C. § 103

Claims 32, 34, 37-39, 44, 46, 49-51, 56, 58, 60-63, 66, 69, 74, and 79 were rejected under 35 U.S.C. § 103 as being unpatentable over Berg et al. (WO 96/07432), in view of Chen et al. (U.S. Patent 5,445,608). Applicant's analysis focuses primarily on independent Claims 32, 44, and 56 because dependent claims 34, 37-43, 46, 49-55, 58, 60-69, 73, 74, 78, 79, and 83 include all the features of these claims. Applicant notes that Claims 32, 44, and 56 have been amended in response to the Advisory Action, and that all amendments are fully supported by the specification.

Independent Claim 32, as presently amended, recites a method of perforating a membrane, comprising bringing a membrane-denaturing substance into contact with or close proximity to at least a site of said membrane, providing a stimulus to the substance so as to

denature a selected site of the membrane, and perforating the denatured selected site of the membrane with a membrane-destroying member, where the membrane recovers to the state prior to perforation. The membrane is a cell membrane, intracellular membrane, or artificial lipid membrane. The substance is a photosensitizer or photocatalyst. The stimulus is light and the light is carried through the membrane-destroying member from a light source.

Independent Claim 44, as presently amended, recites a method of perforating a membrane, comprising bringing a membrane-denaturing substance into contact with or close proximity to at least a site of the membrane, the bringing done by a supporting member for supporting the substance, and providing the stimulus to the substance so as to denature a selected site of the membrane and perforate the denatured selected site of the membrane, where the membrane recovers to the state prior to perforation. The membrane is a cell membrane, intracellular membrane, or artificial lipid membrane. The substance is a photosensitizer or photocatalyst. The stimulus is light, and the light is carried through the supporting member from a light source.

Independent Claim 56, as presently amended, recites a method of perforating a membrane, comprising bringing a membrane-denaturing substance into contact with or close proximity to at least a site of the membrane, and providing the stimulus to the substance so as to denature a selected site of the membrane and perforate the denatured selected site of the membrane, where the membrane recovers to the state prior to perforation. The membrane is a cell membrane, intracellular membrane, or artificial lipid membrane. The substance is a photosensitizer or photocatalyst. The stimulus is light. The light is carried through a stimulus-carrying member from a light source, and the stimulus-carrying member locally introduces the stimulus to the selected site of the membrane.

Support for the amendments to Claims 32, 44, and 56 may be found in the Summary of the Invention section, page 3, the first paragraph under the heading; see also page 14, lines 1-8.

The Examiner states that the method of Berg includes illumination of photosensitizers that generate reactive oxygen species that subsequently damage membranes. The Examiner states that when this process occurs, for example in a lysosome, the contents of the lysosome are released, indicating perforation of the lysosome membrane (Advisory Action, Continuation Sheet).

Berg discloses a method of transporting molecules into the cytosol of living cells by exposing the cells to a photosensitizing compound. The photosensitizing compound is taken up by the cells and located in endosomes or lysosomes. Next, the cells are exposed to light of a suitable wavelength to activate the photosensitizing compound such that the endosomal, lysosomal or other intracellular compartment membranes rupture and molecules are released into the cytosol (Berg, page 5, line 21 to page 6, line 3).

Berg's method requires the cells to be incubated in a solution containing the photosensitizing compound (Examples 1 and 2, pages 8-9). The method relies on the cellular process of endocytosis to bring the photosensitizer and the molecules of choice from the incubating solution into the same cell vesicle (Fig. 1 description, page 3) prior to activation of the photosensitizing compound. According to Berg, "all tissues can be treated *as long as the photosensitizer is taken up by the target cells*" (page 6, lines 21-22, emphasis added).

Berg does not disclose providing a stimulus to a membrane-denaturing substance so as to denature a selected site of the membrane, as now recited in amended Claims 32, 44, and 56. Berg also fails to disclose perforating the denatured selected site of the membrane, as now recited in amended Claims 32, 44, and 56. It would not be possible under Berg to denature a selected site of the membrane, because Berg's method (1) requires all the target cells to be incubated, (2) is only effective on cells that take up the photosensitizer, and (3) is only capable of rupturing intracellular compartments that contain the photosensitizer following endocytosis.

Therefore, Berg's method that relies on the cellular process of endocytosis differs from a method of perforating a denatured selected site of a membrane, defined by Claims 32, 44, and 56.

The Examiner states that Chen discloses an apparatus that allows the delivery to cell membranes of photosensitizers that result in perforation of cell membranes (Advisory Action, Continuation Sheet).

Chen discloses a method and apparatus for photodynamic therapy of tissue by supplying light to a treatment site that has absorbed a photoreactive agent perfused into it (Col. 1, lines 6-11). Chen discloses a catheter that is disposed within a patient's body to supply photoreactive agent to the site of treatment (Col. 4, lines 7-16) and an optical fiber as a light source than can be placed within the catheter in the annular flow channel (Col. 23, lines 43-53).

Chen does not disclose providing a stimulus to a membrane-denaturing substance so as to denature a selected site of the membrane, as now recited in amended Claims 32, 44, and 56. Chen also fails to disclose perforating the denatured selected site of the membrane, as now recited in amended Claims 32, 44, and 56. Instead, Chen discloses "infusing the photoreactive agent into the treatment site" (Col. 5, lines 10-11). It would not be possible under Chen to denature a selected site of the membrane, because Chen's method (1) requires perfusing the entire treatment site, and (2) works on all cells that take up the photoreactive compound. Therefore, Chen's method differs from a method of perforating a denatured selected site of a membrane, defined by Claims 32, 44, and 56.

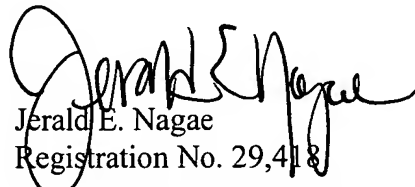
To establish a prima facie case of obviousness, all of the claim limitations must be taught or suggested by the cited prior art. Berg hypothetically combined with Chen fails to teach or suggest all of the claim limitations of the present invention, specifically *providing a stimulus to the substance so as to denature a selected site of the membrane, or perforating the denatured selected site of the membrane*, as now recited in Claims 32, 44, and 56.

Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully submits that all pending claims are in condition for allowance. If the Examiner has any questions, the Examiner is invited to contact Applicant's attorney at the number provided below.

Respectfully submitted,

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July 21, 2016 Janet M. Berdino